Immune Checkpoint Blockade in Cancer Therapy: New Insights and Opportunities

Jim Allison
Ludwig Center for Cancer Immunotherapy
Howard Hughes Medical Institute
Department of Immunology
Memorial Sloan-Kettering Cancer Center

2010 Smalley Lecture
iSBTc
Inventor of intellectual property held by the University of California, Berkeley, licensed to Bristol Meyers-Squibb and Pfizer

Consultant for Bristol Meyers-Squibb
Localization of CD28 and CTLA-4 to the T Cell-APC Interface

CD28

CTLA-4

~ 5 minutes
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CD28

CTLA-4
CTLA-4 Blockade Enhances Tumor-Specific Immune Responses

Attenuated or Terminated Proliferation

Unrestrained Proliferation

Tumor

APC

Necrotic Death
Vaccines
Chemotherapy
Irradiation
Hormone therapy
Anti-angiogenesis
Antibodies
“Targeted” Therapies

TCR

CD28

CTLA-4

Peptide/MHC

B7-1,2
Anti-CTLA-4 Induces Regression of Transplantable Colon Carcinoma

Average Tumor Size (mm²)

Days After Tumor Injection

Rx

Anti-CD28

No Rx

Anti-CTLA-4
Anti-CTLA-4 and GM-CSF Tumor Cell Vaccine Synergize to Eradicate Established B16 Melanoma

- No Rx
- GM-Vaccine
- Anti-CTLA-4
- Both

Average Tumor Size (mm²)

Days After Tumor Injection
anti-CTLA-4/GVAX therapy activates the tumor vasculature and increases infiltration of tumors by CD4 and CD8 effector cells
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\textbf{αCTLA-4/GVax Increases Teff/Treg Ratio In Tumor}

\begin{align*}
\text{CD4/Foxp3} & \quad \text{CD8/Foxp3} \\
\text{untreated} & \\
\text{GMVax/αCTLA-4} & \\
\text{tumor} & \\
\text{GMVax/αCTLA-4} &
\end{align*}

\text{Quezada}
Effective Combinations using anti-CTLA-4 Against Poorly Immunogenic Tumors

**Immunotherapies**
- Gvax: B16 melanoma, TRAMP CaP
- Peptide-pulsed (mugp100) DCs: B16 melanoma
- DNA Vaccine (huTRP2): B16 Melanoma
- Prior depletion of CD25+ cells + vaccine: B16 melanoma
- Adoptive T cell Transfer: B16 melanoma

**Conventional therapies**
- Chemotherapy (cisplatin): Mammary carcinoma
- Local Irradiation: Mammary carcinoma
- Androgen deprivation: TRAMP CaP
- Surgical reduction: TRAMP CaP
- Cryoablation: TRAMP CaP
- Targeted Therapies (17AAG): TRAMP CaP

*Most Anything that kills tumor cells or primes T cells*
Ipilimumab (Bristol-Myers Squibb)

>4,000 patients treated to date:

- Metastatic Melanoma: Data from second line phase III trial is at FDA, first line Phase III completed, awaiting data analysis.

- Castrate-resistant Prostate Cancer: Phase II trials completed, randomized Phase III open

- Objective responses in ovarian, lung, kidney cancer
Ipilimumab: Summary of Clinical Experience

•~15% (RECIST, mWHO) in melanoma as monotherapy, some are complete responses

•Survival benefit in ~35-40% of patients

•Responses are durable:
  Months to years without retreatment, although maintenance treatment is possible
Evolution of Response: Patient Example

Screening

Week 12
Initial increase in total tumor burden (mWHO PD)

Week 16
Responding

Week 72
Durable & ongoing response without signs of IRAEs

20006

Harmankaya
Ipilimumab Pattern of Response: Responses After the Appearance and Subsequent Disappearance of New Lesions

Pre-treatment

Week 12: Progression

10 mg/kg ipilimumab Q3W X 4

New lesions

May, 2007

Source: 2008 ASCO
Abstract #3020 Wolchok.

Wolchok (MSKCC)
Ipilimumab Pattern of Response: Responses After the Appearance and Subsequent Disappearance of New Lesions

Pre-treatment

Week 12: Progression
10 mg/kg ipilimumab Q3W X 4
New lesions

Week 20: Regression

Week 36: Still Regressing

May, 2007

Source: 2008 ASCO Abstract #3020 Wolchok.
Wolchok (MSKCC)
Kaplan-Meier Analysis of Survival

A. Overall Survival

<table>
<thead>
<tr>
<th>Survival Rate</th>
<th>Ipi + gp100 N=403</th>
<th>Ipi + pbo N=137</th>
<th>gp100 + pbo N=136</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>44%</td>
<td>46%</td>
<td>25%</td>
</tr>
<tr>
<td>2 year</td>
<td>22%</td>
<td>24%</td>
<td>14%</td>
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ASCO 2010, Hodi et al. NEJM 2010
Kaplan-Meier Analysis of Survival

A  Overall Survival

Survival Rate | Ipi + gp100 N=403 | Ipi + pbo N=137 | gp100 + pbo N=136
--- | --- | --- | ---
1 year | 44% | 46% | 25%
2 year | 22% | 24% | 14%

ASCO 2010, Hodi et al. NEJM 2010
Subject 3020: Resolution of Prostate Mass

Screening

14 months

Medarex and BMS
Critical Questions for Further Clinical Development of anti-CTLA-4

• What are the cellular and molecular mechanisms involved in the anti-tumor effect?

• What distinguishes responders from non-responders?

• What are the best conventional therapies or vaccines to be used combinatorially?
Cancer Testes (CT) Antigens

- ~100 known family members
- Expressed during germ cell development in immune privileged sites, but not in other normal tissues
- Expressed in many cancer types
- Spontaneous immune responses against these antigens can be detected in some cancer patients
NY-ESO-1 Antibody May Correlate with Clinical Responses In Metastatic Melanoma patients

Clinical Responders

<table>
<thead>
<tr>
<th>Treatment Time Points</th>
<th>NY-ESO-1</th>
<th>LAGE-1</th>
<th>MAGE-4</th>
<th>CT7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wk7</td>
<td>1 TAT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wk12</td>
<td>2 AN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wk45</td>
<td></td>
<td></td>
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<tr>
<td>Pre</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Wk36</td>
<td></td>
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Clinical Non-Responders

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<tr>
<td>Pre</td>
<td>3 RY</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Wk7</td>
<td>8 ABK</td>
<td></td>
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</tr>
<tr>
<td>Wk12</td>
<td>4 PLL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wk35</td>
<td>11 RR</td>
<td></td>
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</tr>
<tr>
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<td>15 DD</td>
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<td></td>
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Legend:
- NY-ESO-1
- LAGE-1
- MAGE-4
- CT7
- CT47
- SOX2
- XAGE-1

Gnjatic & Wolchok
Correlation of NY-ESO-1 antibody with clinical course following anti-CTLA-4 treatment

Patients with NY-ESO-1 antibodies at any time point during study

<table>
<thead>
<tr>
<th>Response</th>
<th># patients Status at wk24 (%)</th>
<th># NY-ESO-1 SERONEGATIVE Status wk24 (%)</th>
<th># NY-ESO-1 SEROPOSITIVE Status wk24 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>6 (5.1%)</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>PR</td>
<td>14 (12.0%)</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>SD</td>
<td>25 (21.4%)</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td><strong>Clinical Benefit</strong></td>
<td><strong>45 (38.5%)</strong></td>
<td><strong>32 (33.7%)</strong></td>
<td><strong>13 (59.1%)</strong></td>
</tr>
<tr>
<td><strong>No Clinical Benefit</strong></td>
<td><strong>72 (61.5%)</strong></td>
<td><strong>63 (66.3%)</strong></td>
<td><strong>9 (40.9%)</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>117 (100%)</td>
<td>95</td>
<td>22</td>
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According to Immune-related response criteria:

CR: Complete Response  
PR: Partial Response  
SD: Stable Disease  
POD: Progression of Disease (includes MR: mixed response)  
DOD: Dead of Disease

Fisher's exact test:  
P value 0.0498

Gnjatic & Wolchok, Ludwig Center/MSKCC  
Halaban and Sznol, Yale
Neoadjuvant anti-CTLA-4 trial in Bladder Cancer

Week - 4 to -1

Ipilimumab Dose

8

Surgery

Blood & Tumor

Blood & Tumor (if feasible)

Blood

Blood

Blood & Tumor

Blood & Tumor

Padmanee Sharma, MDACC
Tissue Analysis

Core biopsy (~ 1 cm x 1mm x 1mm)

TIL expansion

Fine needle aspiration and chunks

IF in frozen sections

Histology sections

IHC in paraffin sections
Bladder:
ICOS expression is higher in tumor tissues from anti-CTLA-4 treated patients

Non-malignant tissues: untreated

Tumor tissues: untreated

Tumor tissues: anti-CTLA-4

Liakou et al., *Proc Natl Acad Sci*, 2008

Sharma, MDACC
Blood:
ICOS$^{\text{high}}$ CD4 T cells in Blood of Bladder Cancer Patients after anti-CTLA-4 Treatment

Pre-therapy

Post-therapy week 3

Post-therapy week 7

Sharma, MDACC
ICOS$^{hi}$ T cells from peripheral blood recognize NY-ESO-1 tumor antigen and produce IFN$\gamma$
Kaplan-Meier curve of overall survival (OS) for melanoma patients receiving ipilimumab therapy.

- Persistent CD4^+ICOS$^{hi}$ increase
- Transient/no CD4^+ICOS$^{hi}$ increase

Median survival for ICOS$^{hi}$ and ICOS$^{lo}$ is 20 months & 8.1 months.

Updated from Carthon et al. Clin Cancer Res 2010
What is the functional significance of ICOS expression after CTLA-4 blockade?
ICOS and ICOS-ligand knockout mice have impaired tumor rejection after anti-CTLA-4 therapy.
Ivax: A novel way of enhancing the effectiveness of CTLA-4 Blockade

Average Tumor Burden

- Untreated
- B16-mlCOSL
- μCTLA-4
- B16-mlCOSL+αCTLA-4

Tumor Volume (mm³)

Days post tumor challenge

Percent survival

Days post tumor challenge
Extended B7-CD28 Family

PD-L1

PD-L2

B7h

B7-1

B7-2

CD28, CTLA-4

B7x

B7-H3

PD-1

ICOS

?
Phase II Trial of anti-PD-1 (MDX-1106)

21 patients, diverse cancer types (5 CC, 2 NSCLC, 8 MEL, 5 HRPC, 1 RCC)

1 complete response, 5 partial responses

Limited toxicity
Why study combination blockade of CTLA-4 and PD-1?

Blocking one co-inhibitory receptor leads to upregulation of the other.

CTLA-4 and PD-1 inhibitory signals are non-redundant.

CTLA-4-/- Mice: 2-3 Weeks -> Lethal Lymphoproliferation

PD-1-/- Mice: 5 Months (Balb) >14 Months (B6) -> Cardiomyopathy (Balb) Lupus (B6)
Blockade of PD-1 Pathway Synergizes with CTLA-4 Blockade

**Tumor Growth**

- Untreated
- 9H10+ratIgG
- 9H10+PD-L1+PD-L2

**Overall Survival**

- Untreated
- 9H10+ratIgG
- 9H10+PD-L1+PD-L2

Quezada
B7-H4 (B7x) and B7H3

• Co-inhibitory *in vitro*

• Expressed at low levels in many tissues

• Not expressed by antigen-presenting cells

• May play a role in tissue defense against autoimmune attack

• Expressed by many tumor cell types

• Soluble form in serum of prostate and renal cancer patients
Increased Expression of B7x in Pancreatic Islets of RIPB7x Transgenic Mice

A

RipB7x transgenic

B

B7x.RQ

PLN spleen pancreas

C

WT

TG
Overexpression of B7x in Pancreas in BDC2.5 Mice Prevents Diabetes
Overexpression of B7x in pancreatic islets inhibits IFN-γ and IL-17 production by BDC2.5 T cells

Intracellular cytokine staining of pancreatic islets

- BDC2.5\(^{+}\)RipB7x\(^{-}\)
- BDC2.5\(^{+}\)RipB7x\(^{+}\)

IFN-γ and IL-17 staining with Vβ4 expression.
Hi level expression of B7x/H3 in prostatectomy samples (n=803) correlates with:

- Extracapsular extension and non-organ confined disease at time of prostatectomy
- Higher risk of clinical failure (metastasis)
- Higher risk of death within 7 years of surgery

Zang et al. PNAS 2007
Extended B7-CD28 Family

- **Limits Responses**
  - PD-L1
  - PD-1
  - PD-L2

- **Inhibit Effector Function**
  - B7x
  - B7-H3

- **Promotes Survival**
  - ICOS

- **Inhibits Proliferation**
  - CD28, CTLA-4

- B7-1, B7-2

- Question marks indicate unknown or variable factors.
Implications for Cancer Vaccines

Don’t worry about:

• Variegated expression of antigens that are targeted by vaccines
• Whether vaccine targets are essential to the tumor survival
• Clonality of transferred T cells

Because death of cells should lead to cross-priming with a battery of other antigens which should be enhanced by checkpoint blockade
Extended B7-CD28 Family

Limits Responses

PD-I
PD-L1
PD-L2

B7x
B7-H3

B7-1
B7-2

ICOS
?

Promotes Survival

Inhibit Effector Function

CD28, CTLA-4

Inhibits Proliferation
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Implications for “Immunosupportive” Therapies

Genomic instability is the bane of targeted therapies, but a goldmine for the immune system

Agents that kill tumor cells (chemotherapy, radiation, hormone therapy, “targeted” therapies) can be considered vaccines

Use with checkpoint blockade to unleash the immune system to maximize T cell responses to multiple targets (turn 1 target into 6)
17-AAG plus CTLA-4 blockade is Effective In Treatment of TRAMP-C2 Prostate Tumors

C57/Bl6 mouse
Tramp

17-AAG
- HSP 90 inhibitor
- Blocks antigen presentation

Tumor (mm³)

Day (s/p tumor inoculation)
Ludwig Center for Cancer Immunotherapy

Jedd Wolchok
Lloyd Old
Pam Sharma

Sacha Gnjatic

Jianda Yuan & the IMF Crew